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Kristina Borror, Ph.D.
Director
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Office for Human Research Protections
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Dear Drs. Menikoff and Borror:

We hereby request that the Office for Human Research Protections (OHRP) promptly conduct a compliance oversight investigation of the following ongoing research study, which is entirely supported by the Department of Health and Human Services (HHS), for all institutions engaged in the research:

> Title: *Effects of Canakinumab on the Progression of Type 1 Diabetes in New Onset Subjects*[1]
> Sponsor: National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

We allege that the above-referenced study is unethical and fails to satisfy the requirements of the HHS human-subjects protection regulations at 45 CFR Part 46, Subpart D ("Additional Protections for Children Involved as Subjects in Research"). In particular, the study, which is enrolling subjects with type 1 diabetes mellitus as young as age 6 years and involves much greater than minimal risk, does not satisfy the requirements of the HHS regulations at 45 CFR 46.404, 46.405, or 46.406. Also, the study has not been approved in accordance with the requirements of 45 CFR 46.407.

The following discussion provides a detailed overview of the rationale for our allegations.

Background on canakinumab and its serious, life-threatening risks

Canakinumab, a potent immunosuppressive drug, is a monoclonal antibody that targets interleukin-1β. It was approved by the Food and Drug Administration (FDA) in June 2009 for the treatment of Familial Cold Autoinflammatory Syndrome and Muckle-Wells Syndrome, rare and potentially life-threatening genetic disorders also known as cryopyrin-associated periodic syndromes (CAPS). The drug has a very long half-life, with prolonged pharmacodynamic effects.[2]

Novartis recently submitted a supplemental Biologics License Application (sBLA) for canakinumab to the FDA for the indication of treating patients with acute attacks of gouty arthritis.[2]

In a briefing document prepared for the June 21, 2011 meeting of the FDA's Arthritis Advisory Committee (ACC) at which the sBLA for canakinumab was considered, the agency described numerous serious safety concerns associated with canakinumab use during the clinical trials conducted in subjects with gouty arthritis. These safety signals are particularly concerning because the number of subjects in the gouty arthritis trials was relatively small and most subjects received a single dose of canakinumab. The overall percent of subjects experiencing at least one serious adverse event was more than two-fold higher in the pool of study subjects receiving canakinumab versus those receiving triamcinolone, one of the standard, FDA-approved treatments for acute gout attacks (see the Table below). Importantly, among the serious adverse events, the occurrence of serious infections was **observed exclusively in the canakinumab treatment groups.**[3]

Table: Overview of Adverse Events in the Canakinumab Trials for Gouty Arthritis

	Canakinumab 150 mg N=253	Triamcinolone N=286
Number of Subjects with at Least 1 AE	**158 (62.5%)**	**145 (50.7%)**
Number of Subjects with at Least 1 Serious AE	**18 (7.1%)**	**9 (3.1%)**
Number of Subjects with at Least 1 Serious Infection	**4 (1.6%)**	**0 (0.0%)**

Given its mechanism of action as an immunosuppressant, canakinumab would be expected to increase the risk of all types of infections. The FDA expressed the following significant concern about this signal for serious infections:

> Although the occurrence of infections would not be unexpected with an IL-1 inhibitor, the increased rate of the serious infections in gout patients after just a single injection of canakinumab is a unique and concerning observation in this development program.[4]

Immunosuppressive drugs, like canakinumab, also can impair the body's immunosurveillance and increase the risk of malignancies, particularly with repeated dosing. The duration and size of the studies involving subjects with gout did not allow for an adequate assessment of the malignancy risk posed by canakinumab to such patients. However, the FDA noted the following concern:

> While the data show that the incidence of malignancies is not increased upon single injection treatment with canakinumab administered for gouty arthritis, the available data do not allow an estimation of the potential risk for malignancies upon chronic repetitive "on demand" canakinumab treatment in the gout population.[5]

Additional abnormalities that occurred more frequently in subjects treated with canakinumab versus subjects treated with triamcinolone during the clinical trials testing canakinumab in patients with gouty arthritis included:[6]

- Leukopenia, neutropenia, and thrombocytopenia
- Declines in renal function
- Elevations in serum triglycerides and total cholesterol
- Elevations in serum uric acid
- Liver dysfunction

Given the serious safety concerns identified during the gouty arthritis trials, the AAC recommended against approval of canakinumab for treating patients with gouty arthritis.

Overview of the NIDDK-supported study of canakinumab in type 1 diabetes mellitus

This study is a multicenter, randomized, double-blind, placebo-controlled trial. Approximately 66 subjects, age 6 to 45 years, with newly diagnosed type 1 diabetes mellitus, all of whom are receiving standard intensive diabetes treatment with insulin and dietary management, are to be randomly assigned to either canakinumab (2.0 milligrams/kilogram) or placebo subcutaneous injections monthly for 12 months (a total of 12 doses). The primary outcome measure is the C-peptide response to a mixed-meal tolerance test. C-peptide is a protein released into the bloodstream by the same cells in the pancreas that make insulin and is used as a marker of how much insulin the pancreas is able to produce. After a meal, C-peptide levels increase in normal people but are low or undetectable in patients with type 1 diabetes mellitus.

Given the known serious risks of even a single dose of canakinumab, including the documented risk of life-threatening infections and the possible risk of malignancies because of the marked immunosuppression, and given the apparent absence of any preliminary data suggesting canakinumab presents the prospect of direct benefits to adults or children with type 1 diabetes mellitus, it is unclear how any institutional review board (IRB) could have approved this study for involvement of children under the HHS

regulations at 45 CFR Part 46, Subpart D ("Additional Protections for Children Involved as Subjects in Research").

Since this research clearly involves much greater than minimal risk, it does not satisfy the requirements for approval under the HHS regulations at 45 CFR 46.404 ("Research not involving greater than minimal risk") or at 45 CFR 46.406 ("Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition"). Therefore, the study may be conducted only if it satisfies the requirements under the HHS regulations at 45 CFR 46.405 ("Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects") or at 45 CFR 46.407 ("Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children").

With respect to the HHS regulations at 45 CFR 46.405, an IRB may approve the study only if the IRB makes and documents all of the following required findings:

- The risk is justified by the anticipated benefit to the subjects;
- The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and
- Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in 45 CFR 46.408.

Given the known serious risks of canakinumab and the absence of data in humans suggesting that canakinumab presents the prospect of any benefits to patients with type 1 diabetes mellitus, there is no reasonable basis on which to affirm the first two required findings cited above.

With respect to the HHS regulations at 45 CFR 46.407, the research may be conducted only if the Secretary of HHS, after consultation with a panel of experts in pertinent disciplines (e.g., science, medicine, education, ethics, and law) and following opportunity for public review and comment, determines either of the following:

- That the research in fact satisfies the conditions of 45 CFR 46.404, 46.405, or 46.406, as applicable, or
- That the following conditions are met:
    - The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;
    - The research will be conducted in accordance with sound ethical principles; and

- Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth in 45 CFR 46.408.

To our knowledge, this study was not approved in accordance with the requirements of 45 CFR 46.407.

We therefore call upon the OHRP to promptly investigate the adequacy of the IRB review for all sites participating in this study and to provide a timely response to the following questions:

- Under what category of research stipulated by 45 CFR Part 46, Subpart D did the IRBs approve the study?

- Did each IRB make the required determinations under Subpart D and provide a reasonable justification for its determinations?

- Were there any IRBs that refused to approve the study? If so, why?

- Have the IRBs been provided with the safety data from all clinical trials involving canakinumab, including those trials involving gouty arthritis patients?

- Were parents/subjects adequately informed about the nature of this research — particularly with respect to its serious risks and the lack of evidence regarding potential benefits — before parental permission/informed consent was obtained?

We also urge the OHRP to suspend this study until the agency has completed its investigation of our allegations.

Concerns about other ongoing clinical trials with canakinumab

A search on the ClinicalTrials.gov website reveals that Novartis, in what can only be described as a "shotgun" approach to research with this drug, is also conducting numerous other clinical trials of canakinumab in subjects with type 2 diabetes mellitus, cardiovascular disease, osteoarthritis, and polymyalgia rheumatica, among others, with several studies involving repeated dosing over a prolonged time period. We are separately writing to the FDA and asking the agency, given the toxicity seen with a single dose of canakinumab in gouty arthritis, to assess all ongoing clinical trials involving this drug and to determine whether they need to be suspended or terminated since the predictable risks to subjects may outweigh the potential benefits of the research. Furthermore, for any trial allowed to continue, we are asking the FDA to assess whether the informed-consent process has an appropriate and complete disclosure of the known risks of canakinumab, including those safety concerns identified in other trials.

Please note that the OHRP may share our complaint letter, with identifiers, with anyone. We will be posting a copy on our website as well.

We look forward to OHRP's thorough and careful investigation of our allegations. Please contact us if you have any questions or need additional information.

Sincerely,

Michael A. Carome, M.D.
Deputy Director
Public Citizen Health Research Group

Sidney M. Wolfe, M.D.
Director
Public Citizen Health Research Group

cc: Honorable Kathleen Sebelius, Secretary of Health and Human Services

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[1] ClinicalTrials.gov. Canakinumab study in individuals with newly diagnosed type 1 diabetes (anti IL-1). (ClinicalTrials.gov identifier: NCT00947427). http://clinicaltrials.gov/ct2/show/NCT00947427. Accessed on June 30, 2011.

[2] Food and Drug Administration. Briefing materials for the June 21, 2011 Arthritis Advisory Committee meeting. Web page 3. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisDrugsAdvisoryCommittee/UCM259596.pdf. Accessed June 30, 2011.

[3] Food and Drug Administration. Briefing materials for the June 21, 2011 Arthritis Advisory Committee meeting. Web page 54. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisDrugsAdvisoryCommittee/UCM259596.pdf. Accessed June 30, 2011.

[4] Food and Drug Administration. Briefing materials for the June 21, 2011 Arthritis Advisory Committee meeting. Web page 59. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisDrugsAdvisoryCommittee/UCM259596.pdf. Accessed June 30, 2011.

[5] Food and Drug Administration. Briefing materials for the June 21, 2011 Arthritis Advisory Committee meeting. Web page 60. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisDrugsAdvisoryCommittee/UCM259596.pdf. Accessed June 30, 2011.

[6] Food and Drug Administration. Briefing materials for the June 21, 2011 Arthritis Advisory Committee meeting. Web pages 66-78. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisDrugsAdvisoryCommittee/UCM259596.pdf. Accessed June 30, 2011.